

# Incidence, recovery and prevalence of infectious diseases: non-parametric disease model and application to influenza in Germany

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## Abstract

In this work we describe a non-parametric disease model that links the temporal change of the prevalence of an infectious disease to the incidence and the recovery rates. The model is only based on the common epidemiological measures incidence and recovery rate. As an application, the model is used to calculate the prevalence of influenza in Germany for a hypothetical birth cohort during 2001 and 2013.

## Introduction

In mathematically modelling infectious diseases, often compartment models are used. Compartment models divide the population under consideration into disjunct sets of individuals with the same biological characteristics. Prominent examples in infectious disease modelling are the *SI*, *SIS* and *SIRS* models, see for example [1, 2]. The models have in common that they depend on one or more parameters. For instance, all these models need a parameter, mostly called *transmission rate*  $\beta$ , that describes how effective contacts between susceptible and infected persons are with respect to spreading the disease. Biological, chemical and physical properties of infectious agents as well as the behaviour of hosts, susceptible or infected, lead to a variety of possible values of  $\beta$ . Even within the same class of disease the transmission characteristics may vary considerably, which was shown for example in influenza [3]. This may impose practical problems in estimating and predicting the parameters.

In this work we analyse the temporal dynamics of the prevalence of infectious diseases in a non-parametric way. The temporal change of the prevalence is expressed in terms of the incidence and the recovery rate.

## SD-Model

We start with a simple compartment model that divides the population into those who are not infected (susceptible), and those who are diseased (Figure 1). The numbers of persons in the states *Susceptible* and *Diseased* are denoted by  $S$  and  $C$  (cases). The transition rates between the states are the incidence rate  $i$  and the recovery rate  $r$ , which depend on the time variable  $t$ .

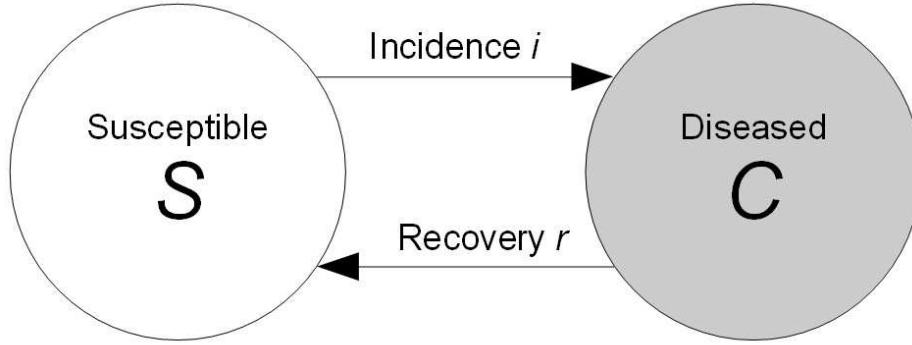


Figure 1: Disease model with two states and the corresponding transition rates. Persons in the state *Susceptible* are healthy with respect to the disease under consideration. After onset of the disease they change into the *Diseased* state. Later they recover and return to the *Susceptible* state.

The equations characterising the changes of  $S$  and  $C$  in the compartment model of Figure 1 are:

$$(1a) \quad \frac{dS}{dt} = -iS + rC$$

$$(1b) \quad \frac{dC}{dt} = iS - rC.$$

By applying the quotient rule to the prevalence  $p = \frac{C}{S+C}$  and inserting these equations we get the following scalar ordinary differential equation (ODE)

$$(2) \quad \frac{dp}{dt} = (1 - p)i - pr.$$

The linear ODE (2) shows that the temporal change  $\frac{dp}{dt}$  of the prevalence is a convex combination of the incidence rate  $i$  and the recovery rate  $r$ . The solution of (2) with the initial condition  $p(t_0) = p_0$  is

$$(3) \quad p(t) = \exp(-G(t)) \left\{ p_0 + \int_{t_0}^t i(\tau) \exp(G(\tau)) d\tau \right\},$$

where

$$G(t) = \int_{t_0}^t i(\tau) + r(\tau) d\tau.$$

**Remark 1:** If  $i$  and  $r$  are constant and the disease is in equilibrium, i.e.  $\frac{dp}{dt} = 0$ , Equation (2) in case of  $p \neq 1$  reads as

$$(4) \quad \frac{p}{1-p} = \frac{i}{r}.$$

This is the well-known result that the prevalence odds  $\frac{p}{1-p}$  equals the product of incidence and mean duration of the disease.

**Remark 2:** For later use we define the triangle function  $\text{tri}_{a,b,h}$ . Let  $a < b$  and  $h > 0$ , then set

$$\text{tri}_{a,b,h}(t) := \begin{cases} h \cdot \left(1 - \frac{2 \cdot |t - \frac{a+b}{2}|}{b-a}\right) & \text{for } a < t < b \\ 0 & \text{else.} \end{cases}$$

The function has a triangular shape with a peak of height  $h$  at  $t = \frac{a+b}{2}$ . An example of a triangle function is the red curve in Figure 3.

## Examples

In this section we illustrate Equations (2) and (3) by some examples.

### Example 1

The first example assumes a rectangular time course of the incidence (Figure 2). The *support* of the incidence (i.e., the set  $\text{supp}(i) := \{t \mid i(t) > 0\}$ ) is  $(5, 10)$ , the support of the recovery rate is  $\text{supp}(r) = (7, 17)$ . On these intervals the values of the incidence and recovery are assumed to be  $4 \cdot 10^{-5}$  and 0.85 (per week), respectively. The resulting prevalence (calculated by numerically integrating Equation (3)) is shown as blue curve in Figure 2.

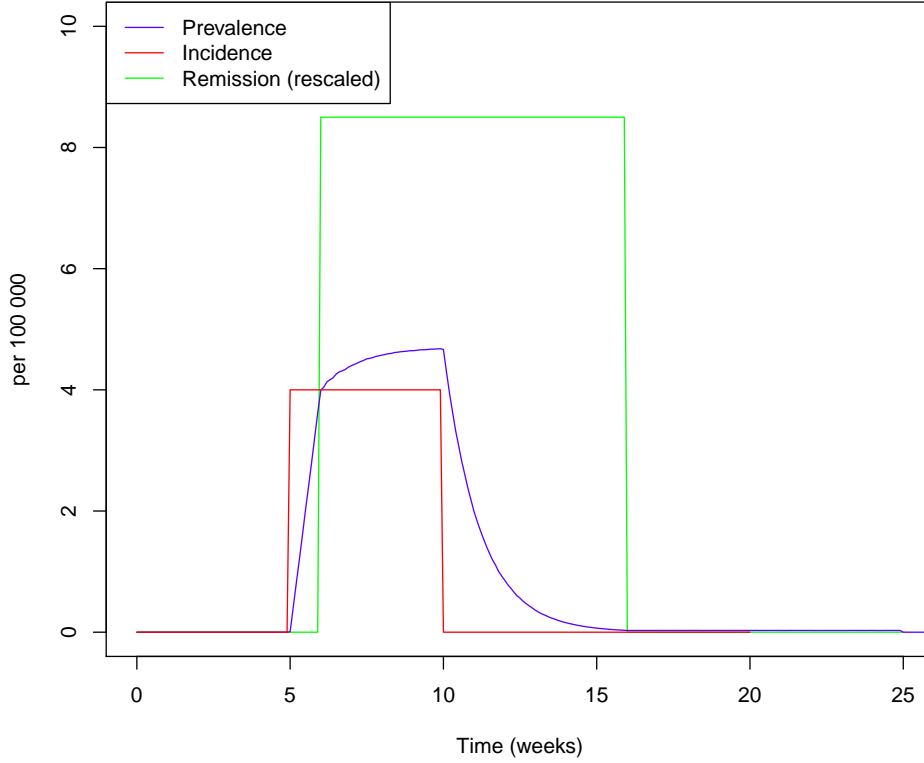


Figure 2: Time course of the incidence (red) and recovery rate (green, rescaled by multiplying with  $10^{-4}$ ) in Example 1. The resulting prevalence according to Equation (3) is the blue curve.

## Example 2

As we shall see in the next section, the time course of the incidence in a wave of influenza does not have a rectangular shape. It is (approximately) symmetric and has a peak in the middle. Compared to the previous example, a triangular shape of the incidence is more realistic. We assume a wave of influenza having the incidence as shown by the red curve of Figure 3:  $i = \text{tri}_{5,15,h}$  with  $h = 1.5 \cdot 10^{-5}$  (per week). The recovery rate  $r$  is assumed to be a triangle function, too, with  $\text{supp}(r) = (6.5, 20)$  and peak height 1.7 (per week). The time course of the associated prevalence (blue line in Figure 3) has been calculated by Equation (3).

From Figure 3 it is apparent that the prevalence starts to increase later than the incidence. At about week 7, the prevalence has overtaken the incidence.

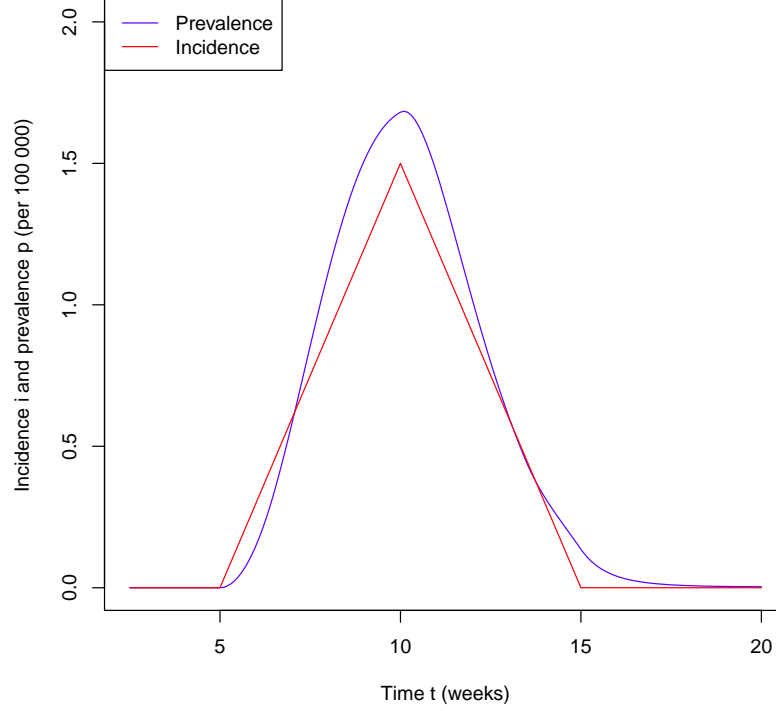


Figure 3: Time course of the incidence rate (red) and prevalence (blue) in Example 2. Note the delay between the incidence and the prevalence.

In week 10 the incidence peaks at  $1.5 \cdot 10^{-5}$  (per week), whereas the prevalence peaks at about 0.3 weeks later at the value  $1.68 \cdot 10^{-5}$ . In summary, we can see that the prevalence is delayed compared to the incidence and overshoots the peak of the incidence.

### Example 3: Equilibrium

To illustrate Equation (4), we have chosen  $i(t) = 10^{-5}$  for  $t \geq 5$  and  $r(t) = 0.2$  for  $t \geq 10$ . The associated duration of the disease is  $\frac{1}{0.2} = 5$ . Beginning at  $t = 10$  the prevalence is constant (equilibrium). It holds  $\frac{p(t)}{1-p(t)} = 5 \cdot 10^{-5}$  for all  $t \geq 10$ . Figure 4 shows the course of the associated prevalence (blue).

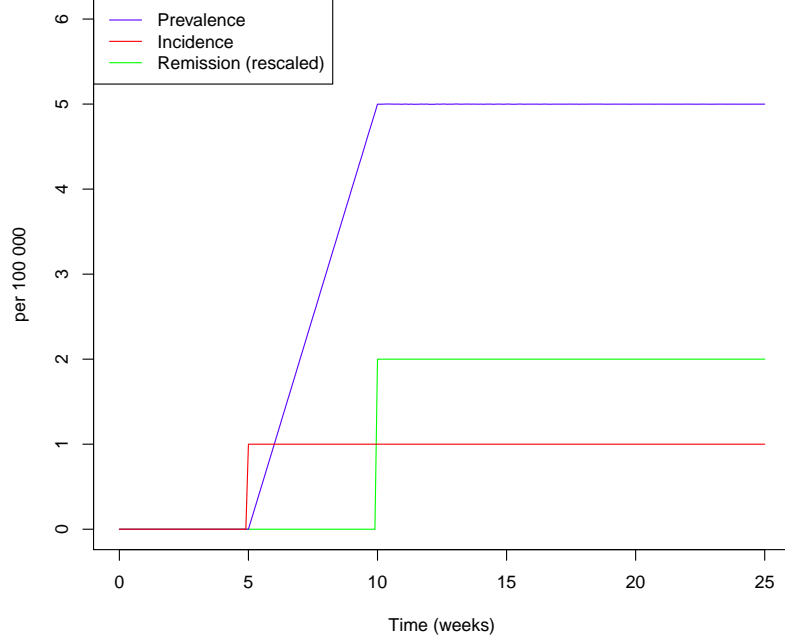


Figure 4: Time course of the incidence rate (red), recovery rate (green, rescaled by multiplying with  $10^{-4}$ ) and prevalence (blue) in Example 3.

### Example 4

For use in the next section we solve the following problem: given the triangular incidence  $i = \text{tri}_{a_1, b_1, h_1}$ ,  $h_1 > 0$ ,  $a_1 < b_1$ , what has to be the minimal  $h_2$  in a triangular recovery  $r = \text{tri}_{a_2, b_2, h_2}$ ,  $h_2 > 0$ ,  $a_2 < b_2$  and  $a_1 < a_2$ ,  $b_1 < b_2$ , such that  $p(T) = 0$  for all  $T \geq b_2$ ? With other words: what is the minimal peak height  $h_2 > 0$  of a triangular recovery rate  $r$  that follows after a triangular incidence  $i$  with height  $h_1$  such that the disease is eradicated at  $T \geq b_2$ .

For  $T \geq b_2$  it holds

$$p(T) = \exp(-G(T)) \int_{a_1}^{b_1} \text{tri}_{a_1, b_1, h_1}(\tau) \exp(G(\tau)) d\tau$$

with

$$G(t) = \int_{a_1}^t \text{tri}_{a_1, b_1, h_1}(\tau) + \text{tri}_{a_2, b_2, h_2}(\tau) d\tau.$$

It is easy to see that  $p(T) = p(b_2)$  for all  $T \geq b_2$ . Thus, we may speak of the *terminal prevalence*. As the terminal prevalence  $p(T)$  is the product of two positive factors, the prevalence is positive for all  $T \geq b_2$ . Hence, the only aim we can achieve is to bring  $p(T)$  below a prescribed threshold. That this is possible, can be seen by the following calculation

$$\begin{aligned} p(T) &= \exp(-G(T)) \int_{a_1}^{b_1} \text{tri}_{a_1, b_1, h_1}(\tau) \exp(G(\tau)) d\tau \\ &\leq \exp(G(b_1) - G(T)) \int_{a_1}^{b_1} \text{tri}_{a_1, b_1, h_1}(\tau) d\tau \\ &= \frac{1}{2} h_1 (b_1 - a_1) \exp(G(b_1) - G(T)). \end{aligned}$$

The inequality holds true, because  $G$  is monotonically increasing. From

$$G(b_1) - G(T) = - \int_{\max(b_1, a_2)}^{b_2} \text{tri}_{a_2, b_2, h_2}(\tau) d\tau = -\frac{1}{2} h_2 (b_2 - \max(b_1, a_2))$$

it follows that  $p(T) \rightarrow 0$  as  $h_2 \rightarrow \infty$ .

For a given incidence  $i = \text{tri}_{a_1, b_1, h_1}$  and  $a_2, b_2$  we are interested in the minimal  $h$  such that the terminal prevalence  $p(T)$  is below a prescribed threshold.

To solve this problem, we examine the function

$$\mathcal{H}_{a_1, b_2, h_1, a_2, b_2} : h \mapsto p(T) = \int_{a_1}^{b_1} \text{tri}_{a_1, b_1, h_1}(\tau) \exp(G(\tau) - G(T)) d\tau,$$

where  $G(t) = \int_{a_1}^t \text{tri}_{a_1, b_1, h_1}(\tau) + \text{tri}_{a_2, b_2, h}(\tau) d\tau$ . Figure 5 gives an example of the terminal prevalence  $p(T)$  for  $a_1 = 5$ ,  $b_1 = 15$ ,  $h_1 = 1.5 \cdot 10^{-5}$  (incidence in Figure 3) and  $a_2 = 6.5$ ,  $b_2 = 20$ .

We will choose the threshold  $h$  such that the terminal prevalence is one per mille of the peak incidence, i.e.  $p(T) \leq \frac{h_1}{1000}$ . Then, we assume that the wave of influenza is eradicated after  $b_2$ . The corresponding peak height  $h_2$  in case of  $a_1 = 5$ ,  $b_1 = 15$ ,  $h_1 = 1.5 \cdot 10^{-5}$  and  $a_2 = 6.5$ ,  $b_2 = 20$  is  $h = 2.20$ .

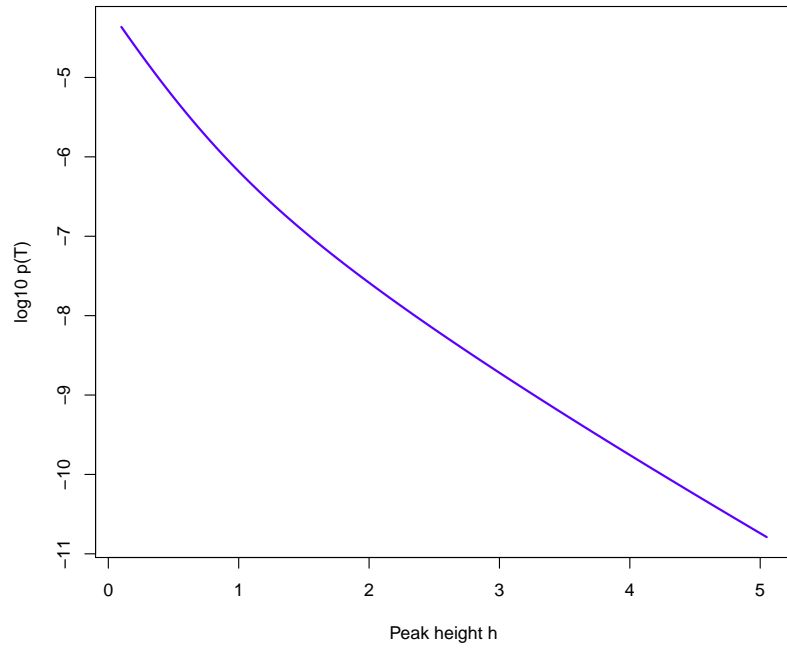


Figure 5: Logarithm of the terminal prevalence  $p(T)$ ,  $T \geq b_2$ , as a function of the peak height  $h$ .



## Influenza in Germany 2001-13

Figure 6 shows the incidence of influenza in Germany from 2001 to 2013. The abscissa and ordinate represent calendar time and age, respectively. The colour indicates the incidence rate, the associated numerical values are coded as shown in the rightmost part of Figure 6. By incidence we mean the incidence reported to the national influenza register at the Robert-Koch-Institute, [4]. In Germany, all confirmed influenza cases statutorily have to be reported to the Robert-Koch-Institute (influenza A, B, C according to the reference definition).

From Figure 6 it becomes apparent that influenza usually appears in the first quarter of the year and vanishes (nearly) completely from the second to the fourth quarter. An exception is the epidemic in the last quarter of 2009. Then, the swine flu (H1N1 influenza) became pandemic. We also see that not all age groups are affected equally from one wave of influenza to the other. It seems that as calendar time progresses, the more older age groups get involved.

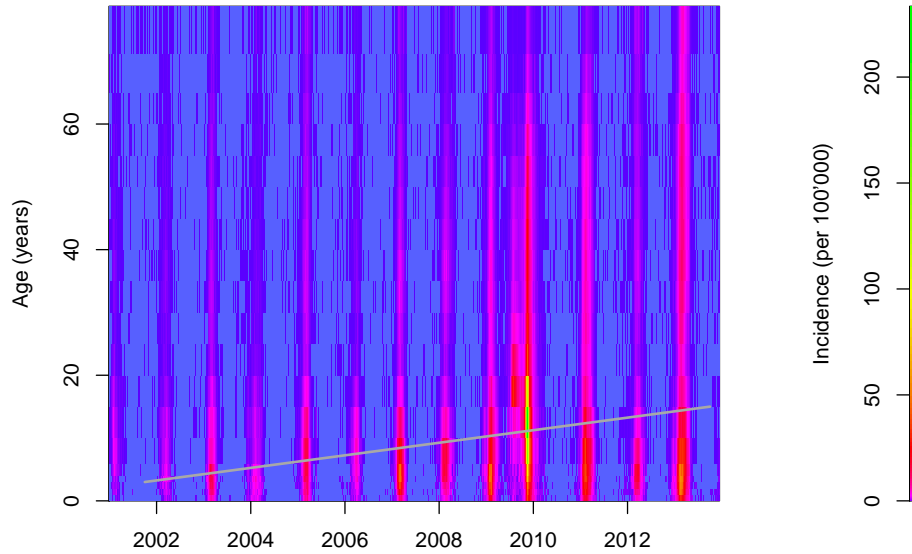


Figure 6: Age-specific incidence of influenza (per 100 000) in Germany 2001-2013. The whitish line in the lower part represents the trajectory of a hypothetical cohort.

In Figure 6 a whitish line is visible in the lower third of the image. This is the trajectory of a hypothetical birth cohort born in September 1998, which has

been followed from September 2001 to September 2013. The values of the incidence rate along the line is shown in Figure 7. The seasonal variability and the enormous peak during the swine flu pandemic are clearly visible.

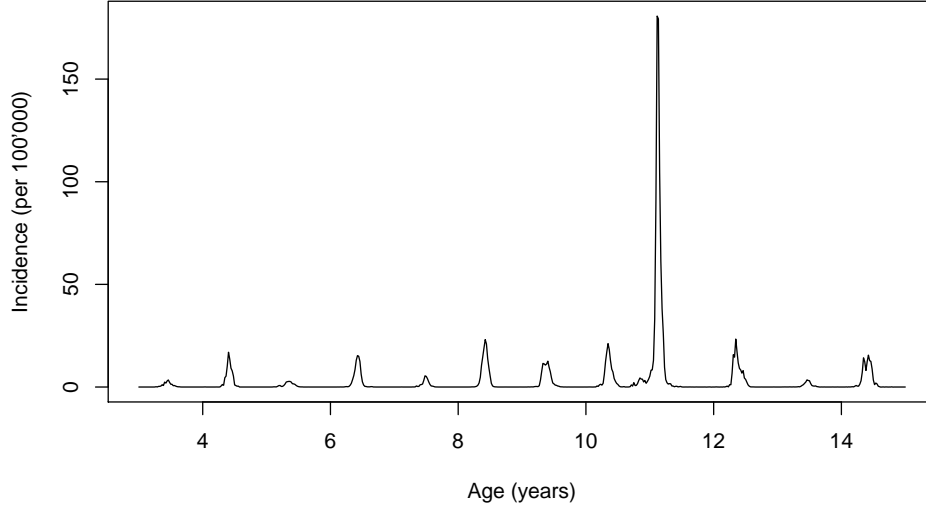


Figure 7: Incidence of influenza for a birth cohort followed up along the whitish line in Figure 6.

During follow-up, the birth cohort faces twelve waves of influenza with different intensities (see Figure 7). Three of them are analysed in more detail: the wave with relatively low incidence at 3.5 years of age (spring 2002), the moderate wave at age 8.5 (spring 2007) and the swine flu at age 11.3 (autumn 2009). The corresponding incidences are shown as black curves in Figure 8. The raw incidence data are approximated by triangle functions  $i_k = \text{tri}_{a_k, b_k, y_k}$ ,  $k = 1, 2, 3$ . These have been calculated by an ordinary least squares approach. As in Example 4 (see above) we assume triangle functions for the recovery rates  $r_k$ ,  $k = 1, 2, 3$ . The support of the recovery rate  $r$  is assumed to be  $a_2 = a_1 + 3/365.25$  and  $b_2 = b_1 + 17/365.25$ . This corresponds to a mean delay of 10 with range 3-17 (days). The peak heights  $h_k$  of the recovery rates  $r_k$  are calculated as in Example 4 by forcing the terminal prevalence to be less than one per mille of the peak incidence. The results are presented in Table 1.

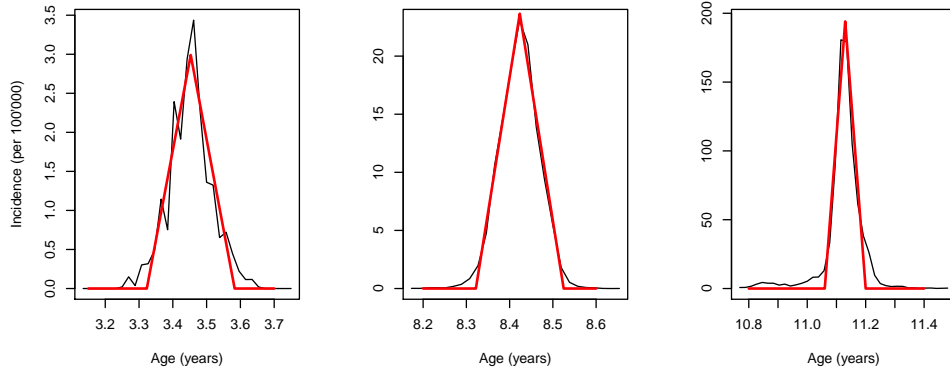


Figure 8: Three influenza waves of the birth cohort in Figure 7: spring 2002 (left), spring 2007 (middle) and autumn 2009 (right). The black curves are the raw incidence rates as reported to the Robert-Koch-Institute [4]. The triangle functions (red) are the approximated incidence rates. Note the different scalings of the ordinate.

Table 1: Analysed influenza waves of the birth cohort and characteristics of the triangular incidence and recovery rates.

Influenza wave	Incidence $i$		Recovery $r$	
	Support $\text{supp}(i)$	Peak height	Support $\text{supp}(r)$	Peak height
Spring 2002	(3.323, 3.583)	$2.99 \cdot 10^{-5}$	(3.350, 3.610)	190.35
Spring 2007	(8.322, 8.525)	$23.7 \cdot 10^{-5}$	(8.349, 8.552)	167.61
Autumn 2009	(11.060, 11.200)	$194 \cdot 10^{-5}$	(11.087, 11.227)	137.85

The time courses of the prevalence during the three waves of influenza are depicted in Figure 9. The shapes are very similar but the peak values differ considerably.

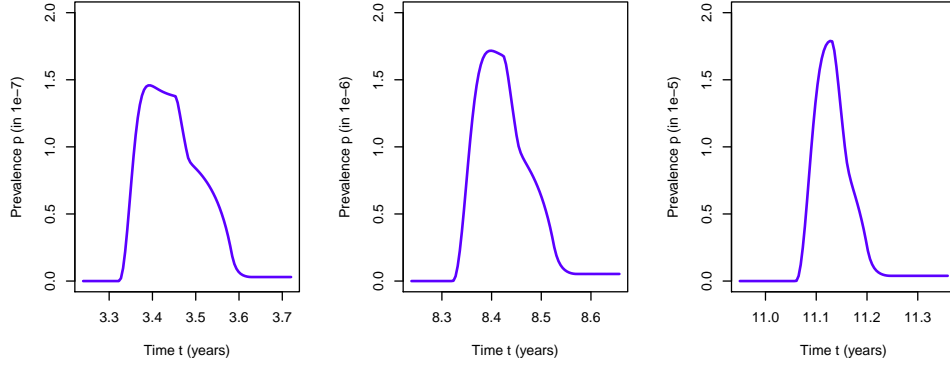


Figure 9: Prevalence of influenza in the birth cohort during the three analysed waves: spring 2002 (left), spring 2007 (middle) and autumn 2009 (right). Note the different scalings of the ordinate.

During the waves in spring 2002 and 2007 the peak prevalence was  $1.458 \cdot 10^{-7}$  and  $1.716 \cdot 10^{-6}$ , respectively. The maximum of the prevalence during the swine flu epidemic in autumn was  $1.790 \cdot 10^{-5}$ . Roughly speaking, the three peak prevalences differ by about one magnitude. This is consistent with the incidence rates, which approximately differ by a factor of 10.

## Discussion

In this work we have described a disease model that links the temporal change of the prevalence to the incidence and the recovery rates. The model is non-parametric in the sense that it does not depend on biological, behavioural or disease-specific parameters. It is only based on the common epidemiological measures incidence and recovery rate. In that respect the model is very flexible and is not restricted to a specific class of infectious disease.

After the introduction of the disease model, the characterising equations and some examples, the model has been applied to incidence of influenza in Germany during 2001-2013. The incidence data stem from the Robert-Koch-Institute, which is the official authority each confirmed case of influenza in Germany by law has to be reported to. Since data about recovery rates are not published, assumptions had to be made. With these assumptions the prevalence of influenza during three waves has been calculated for a hypothetical birth cohort. During the three waves of influenza, the resulting prevalence portions in the birth cohort are low. There are mainly two reasons: the first is the short duration of symptoms of averagely 10 days (range 3-17 days), which implies a high recovery rate with onset soon after the start of the wave of influenza. The second reason lies in the data itself. Presumably, the cases reported to the Robert-Koch-Institute are only the most severe cases. It is very likely that a lot of patients with the symptoms of influenza have not been examined by a medical doctor at all, or have not been examined in detail (for example by PCR). Those cases have not been *confirmed influenza cases* that statutorily have to be reported. Thus, they are not covered by the incidence rates in this article. The fraction of unreported cases is difficult to access and is beyond the scope of this work. Although the equations are mathematically correct in the context they were developed for (no mortality, no migration), due to this coverage issue the calculated prevalence portions have to be interpreted very carefully.

Another limitation of this article lies in the mathematical models for the incidence and recovery rates. Here, we have used rectangle and triangle functions. In countries with seasonal waves of influenza, incidence and recovery rates vanish in certain periods. Thus, in modelling single waves of influenza, functions with bounded support would be preferable. Here, we have chosen triangle and rectangle functions, but other functions may be possible as well, for example B-splines. In regions where influenza is present during the whole year, incidence and remission do not have bounded support.

So far, the model in Figure 1 does not include the impact of mortality. One

may do so by changing the equations in (1):

$$\begin{aligned}\frac{dS}{dt} &= -i S + r C - m_0 S \\ \frac{dC}{dt} &= i S - r C - m_1 C.\end{aligned}$$

Then, Equation (2) changes to

$$(5) \quad \frac{dp}{dt} = (1-p)i - pr - p(1-p)\Delta m,$$

with  $\Delta m = m_1 - m_0$ , [5]. Note that Equation (5) becomes Equation (2) in case of  $m_1 = m_0$ . Here an interesting point becomes obvious: Equation (2) is a consequence of Equation (1). However, while Equation (1) implies  $\frac{d(S+C)}{dt} = 0$ , i.e. the population size remains constant, Equation (2) does not imply this. As it is a special case of Equation (5), Equation (2) holds true in the presence of mortality with  $m_1 = m_0$ .

## References

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